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ORIGINAL RESEARCH

Sufentanil protects against blood-brain barrier injury in rat with intracerebral hemorrhage

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Abstract

Disruption of blood-brain barrier is a common brain injury in intracerebral hemorrhage. Sufentanil is an analogue of fentanyl, and acts as an opioid analgesic in postsurgical analgesia and anaesthesia. Sufentanil also exerted a neuroprotective effect against cerebral infarction. The role of sufentanil in intracerebral hemorrhage (ICH)-induced blood-brain barrier injury was investigated. Firstly a rat model of intracerebral hemorrhage was established by local injection of collagenase IV into striatum. Rats were then subjected to tail vein injection with sufentanil. Results showed that injection with collagenase IV induced histological damages in brain tissues, increased brain water content and enhanced Evans blue leakage. However, administration with sufentanil attenuated behavioral deficits and histological damages in the brain tissues of rats with intracerebral hemorrhage. Moreover, sufentanil also reduced brain water content and inhibited Evans blue leakage. Sufentanil attenuated collagenase IV-induced increased levels of tumor necrosis factor α (TNF-α), interleukin (IL)-6, and IL-1β in rats with intracerebral hemorrhage. Sufentanil suppressed phosphorylation of c-Jun N-terminal kinase (JNK) and P38 in brain tissues of rats with intracerebral hemorrhage. In conclusion, sufentanil exhibited neuroprotective effects on blood-brain barrier injury in rat with intracerebral hemorrhage, and inhibited neuroinflammation through the inactivation of mitogen-activated protein kinase (MAPK) signaling.

Keywords

Sufentanil; Intracerebral hemorrhage; Blood-brain barrier injury; Collagenase IV; Neuroinflammation; MAPK signaling

1. Introduction

Intracerebral hemorrhage (ICH) is a destructive cerebrovascular disease with high mortality and disability, which accounts for 10%–15% of stroke-associated deaths [1]. Risk factors, such as alcohol consumption, diabetes, obesity, and hypertension, can cause rupture of arterial vasculature that leads to leakage of blood into adjacent brain parenchyma, thus resulting in the formation and expansion of hematoma during the development of ICH [2]. Strategies, including matrix metalloproteinases, hemoglobin degradation products, inflammatory mediators, and thrombin, have been widely used in the treatment of ICH [2, 3]. However, there is currently no available pharmacological treatment that provides adequate benefit for patient with ICH [3].

The formation and expansion of hematoma induce primary brain injury during the development of ICH through promoting intracranial pressure and herniation [3]. Moreover, secretion of inflammatory factors, infiltration of peripheral immune cells, and activation of resident cells promote brain edema and cell death to stimulate ICH-related secondary brain injury [3]. Blood-brain barrier, located in microvascular endothelium, consists of neurons, astrocytes, extracellular matrix, pericytes, basement membrane, and vascular endothelial cells, which are connected by tight junctions [4]. The blood-brain barrier is essential for cerebral microvasculature and homeostasis in central nervous system [5]. Disruption of blood-brain barrier by neuroinflammation is the most common brain injury of ICH, aggravating vasogenic brain edema and contributing to the devastating nature of ICH [4]. Therapeutic interventions for blood-brain barrier injury are novel strategies for the treatment of ICH [2].

Sufentanil is an analogue of fentanyl and functions as an agonist to μ-opioid receptor and is widely used in postsurgical analgesia and anaesthesia [6]. Sufentanil has been shown to reduce ischemia/reperfusion-induced cell apoptosis and inflammation in liver [7, 8], and suppress sepsis-induced acute lung inflammation and oxidative stress [9]. Sufentanil also exerts antinociception effects in rats with neuropathic pain [10]. Moreover, sufentanil inhibits neuronal apoptosis and inflammatory responses in rats with cerebral ischemia-reperfusion injury and ameliorated neurological dysfunction and blood-brain barrier injury [11]. Therefore, sufentanil might also exhibit neuroprotective effect on ICH-associated blood-brain

barrier injury.

In this study, the effects of sufentanil on histological damages, blood-brain barrier injury, and neuroinflammation of rats with ICH were investigated.

2. Materials and methods

2.1 Animal model

A total of 84 male Sprague-Dawley rats (6–8 weeks old) weighted 220–250 g, were purchased from Slac Laboratory Animal Co., Ltd. (Shanghai, China). Rats were divided into seven groups: sham, ICH, ICH + 5 μg/kg sufentanil, ICH + 10 μg/kg sufentanil, ICH + 20 μg/kg sufentanil, ICH + 2 μg/kg pyridinyl imidazole (SB202190; MAPKs inhibitor), and ICH + 2 μg/kg SB202190 + 20 μg/kg sufentanil (n = 12 in each group). Rats in the ICH groups were anesthetized to inhale 3% isoflurane (26675-46-7, Sigma-Aldrich, St. Louis, MO, USA), and then placed in a brain stereotaxic apparatus. Skull and bregma were exposed, and cranial burr holes with diameter of 1 mm were drilled in the right part of brain. A microsyringe with a needle tip, stereotactically through the holes, was inserted into the right striatum at coordinates 6.0 mm ventral, 3.5 mm lateral to the bregma, and 0.2 mm posteriorly. Rats were then injected with 2 μL of 0.3 U collagenase type IV (Sigma-Aldrich) that were dissolved in sterile normal saline according as previously reported [12]. After 10 minutes, the needle tip was removed, and then the scalp was sutured. Rats in the sham group underwent the same surgery and were injected with sterile saline instead of collagenase. Six hours later, rats in the ICH + sufentanil group were then subjected to tail vein injection with sufentanil or SB202190 (152121-30-7, Sigma-Aldrich, St. Louis, MO, USA).

2.2 Behavioral assessment

Three days after surgery, a modified neurological severity scores (mNSS) test was performed according to a previous research [13] by two blinded investigators. The mNSS score was recorded from 0 (normal) to 18 (maximal deficit).

2.3 Hematoxylin and eosin staining

Brain tissues were fixed in 10% formalin and then embedded in paraffin after behavioral test. Tissues were sliced into 5 μm sections, and the sections were stained with hematoxylin and eosin (GHS316, HT1101128, Sigma-Aldrich, St. Louis, MO, USA). Histological damages of brain sections were observed under microscope (CX23 RFS1, Olympus, Tokyo, Japan).

2.4 Terminal deoxynucleotidyl transferase dUTP nick-end labeling (TUNEL) staining

Brain sections were deparaffinized with xylene and dehydrated with ethanol. Sections were treated with protein kinase K, and then reacted with TdT and Luciferase-labeled dUTP from TUNEL staining using the *in situ* Cell Death Detection Kit (11684795910, Roche, Basel, BS, Switzerland). The nucleus was stained with DAPI (4′,6-diamidino-2-phenylindole), and the number of TUNEL-positive cells was counted and verified as neuronal apoptosis under microscope. The apoptotic rate was calculated as (number of TUNEL-positive cells/total cells) $\times$100%.

2.5 Assessment of brain water content

Three days after surgery, brain hemispheres of rats in each group were collected and separated into five parts: cerebellum, contralateral basal ganglia, ipsilateral basal ganglia, contralateral cortex, and ipsilateral cortex. Each part was weighed to record the wet weight. All parts were then dried at 100 ℃ for 24 hours, and then weighted to record the dry weight. Brain water content was assessed using a formula: ((wet weight–dry weight)/(wet weight)) $\times$ 100%. The cerebellum was used as an internal control.

2.6 Evans blue staining

Three days after surgery, rats were anesthetized under intraperitoneal injection of chloral hydrate, and then received 15 mg/kg of Evans blue solution (Sigma-Aldrich) through femoral vein injection. The solution was circulated for 3 hours before transcranial perfusion with PBS (phosphate Buffered Saline). Brains were collected and homogenized in PBS. Tissues were sonicated and then centrifuged at 12,000 $\times$ g for 1 hour at 4 ℃. The supernatants were collected and treated with 50% trichloroacetic acid overnight at 4 ℃. The supernatants were centrifuged at 15,000 $\times$ g for 1 hour, and the absorbance at 620 nm was measured using a spectrophotometer (SPECTRONIC 200, 840-281700, Thermo Fisher Scientific, Waltham, MA, USA). Based on the standard curves, the concentrations of evans blue from 100 µg brain samples were determined from the absorbance.

2.7 ELISA

Brains were lysed in radioimmunoprecipitation assay buffer (P0013B, Beyotime, Beijing, China), and the lysates were centrifuged at 12,000 $\times$ g for 1 hour at 4 ℃. Levels of TNF-α (H052-1-2), IL-1β (H002-1-2), and IL-6 (H007-1-1) were detected by ELISA assay kits (Nanjing Jiancheng Bioengineering Institute, Nanjing, Jiangsu, China).

2.8 Western blot

Lysates from brain tissues were separated using sodium dodecyl-sulfate polyacrylamide gel electrophoresis, and then transferred onto nitrocellulose membranes. Membranes were blocked in 5% dry milk, and then incubated with primary antibodies: anti-claudin 3 (ab15102) and anti-occludin (ab31721) (1:2000), anti- Zonula occludens-1 (ZO-1) (ab221546) and anti-β-actin (ab8227) (1:3000), anti-p-p65 (ab76302) and anti-p65 (ab16502) (1:4000), anti-p-P38 (ab4822) and anti-P38 (ab170099) (1:5000), anti-p-JNK (ab76572) and anti-JNK (ab124956) (1:6000). The membranes were then incubated with the secondary antibodies (ab288151) (1:5000), and subjected to chemiluminescence reagent kit (P0018AS, Beyotime, Beijing, China). All antibodies were purchased from Abcam (Cambridge, MA, USA). β-actin was used as a loading control to normalize total protein expression. The blots were quantified using Image J software.

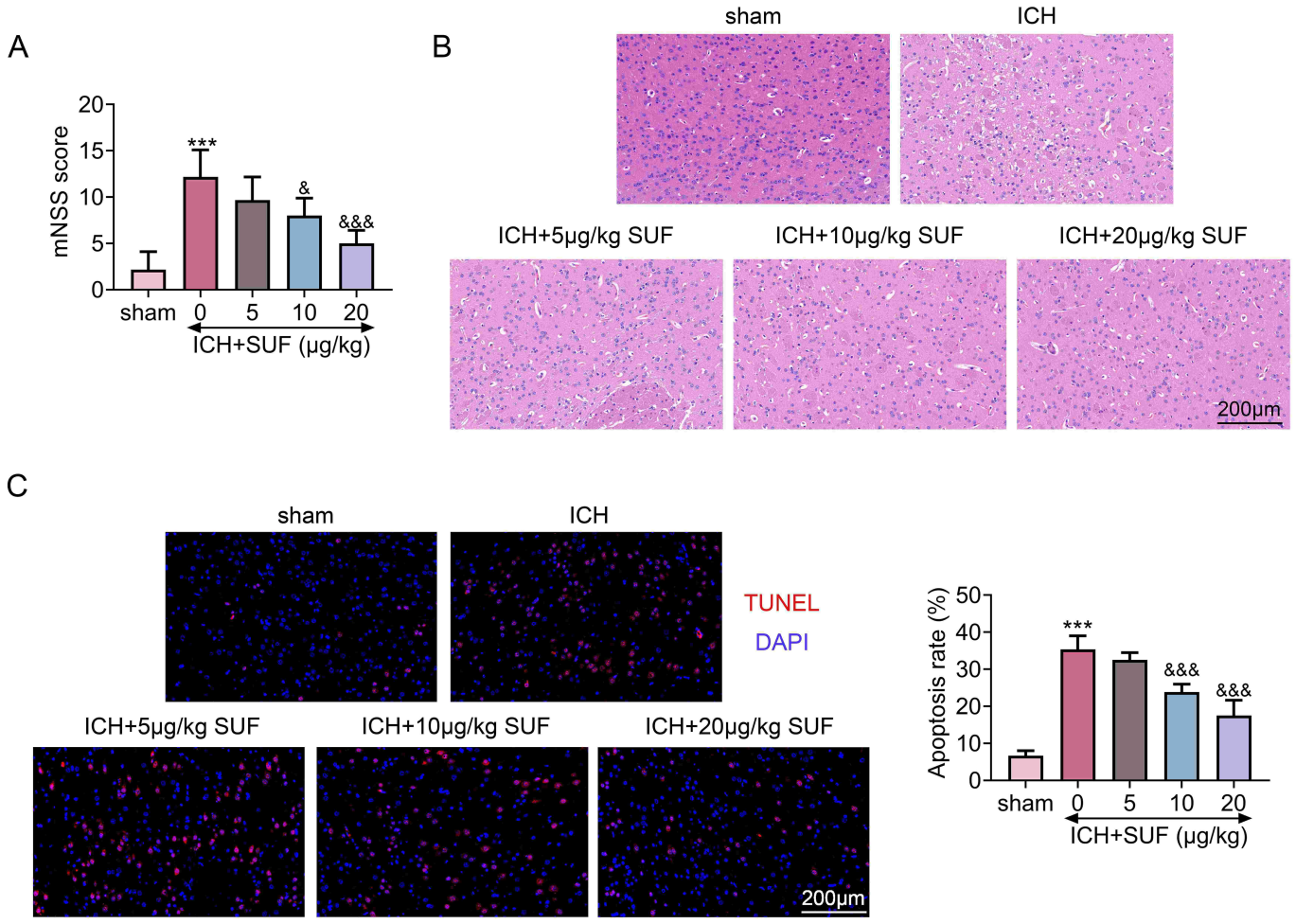

FIGURE 1. Sufentanil ameliorated histological damages of rats with ICH. (A) Sufentanil attenuated collagenase injection-induced increase of mNSS score in rats to attenuate behavioral deficits. N = 12. (B) Sufentanil attenuated intracerebral hemorrhage with mass effects to right lateral ventricle and corpus callosum in rat model of ICH induced by collagenase injection. N = 12. (C) Sufentanil reduced the neuronal apoptosis of rats with ICH. N = 12. *** *vs.* sham, $p < 0.001$. $^{\&}$, $^{\&\&\&}$ *vs.* ICH, $p < 0.05$, $p < 0.001$. ICH: intracerebral hemorrhage; mNSS: modified neurological severity scores; TUNEL: transferase dUTP nick-end labeling; SUF: Sufentanil; DAPI: 4′,6-diamidino-2-phenylindole.

2.9 Statistical analysis

All data were expressed as mean ± standard error of the mean and analyzed by student's *t*-test or one-way analysis of variance under Statistical Product and Service Solutions (SPSS) 11.0 (SPSS Inc., Chicago, IL, USA). $p < 0.05$ was considered as statistically significant.

3. Results

3.1 Sufentanil ameliorated histological damages of rats with ICH

To induce ICH, rats were locally injected with collagenase IV into the striatum. Data from mNSS test showed that injection with collagenase IV significantly increased mNSS score in rats (Fig. 1A). However, administration of sufentanil significantly reduced mNSS score of rats with ICH in a dosage dependent way (Fig. 1A). Brains of rats with ICH demonstrated intracerebral hemorrhage, but sufentanil alleviated the histological damages of rats with ICH (Fig. 1B). Moreover, neuronal apoptosis in brain tissues was significantly induced in rats with ICH, while sufentanil significantly suppressed the neuronal apoptosis of rats with ICH (Fig. 1C).

3.2 Sufentanil ameliorated blood-brain barrier injury of rats with ICH

Injection with collagenase IV induced brain edema through increasing brain water content (Fig. 2A). Evans blue dye leakage was significantly promoted in rats post collagenase IV injection (Fig. 2B). However, sufentanil reduced brain water content (Fig. 2A) and significantly inhibited Evans blue dye leakage (Fig. 2B). Moreover, sufentanil significantly attenuated collagenase IV-induced down-regulation of claudin 3, occludin and ZO-1 proteins in rats (Fig. 2C).

3.3 Sufentanil ameliorated neuro-inflammation of rats with ICH

Injection with collagenase IV significantly up-regulated levels of TNF-α, IL-1β, and IL-6 in the brain tissues of rats, while sufentanil down-regulated the levels of TNF-α, IL-1β, and IL-6 in rats with ICH (Fig. 3A). p65, also known as RelA, is one of

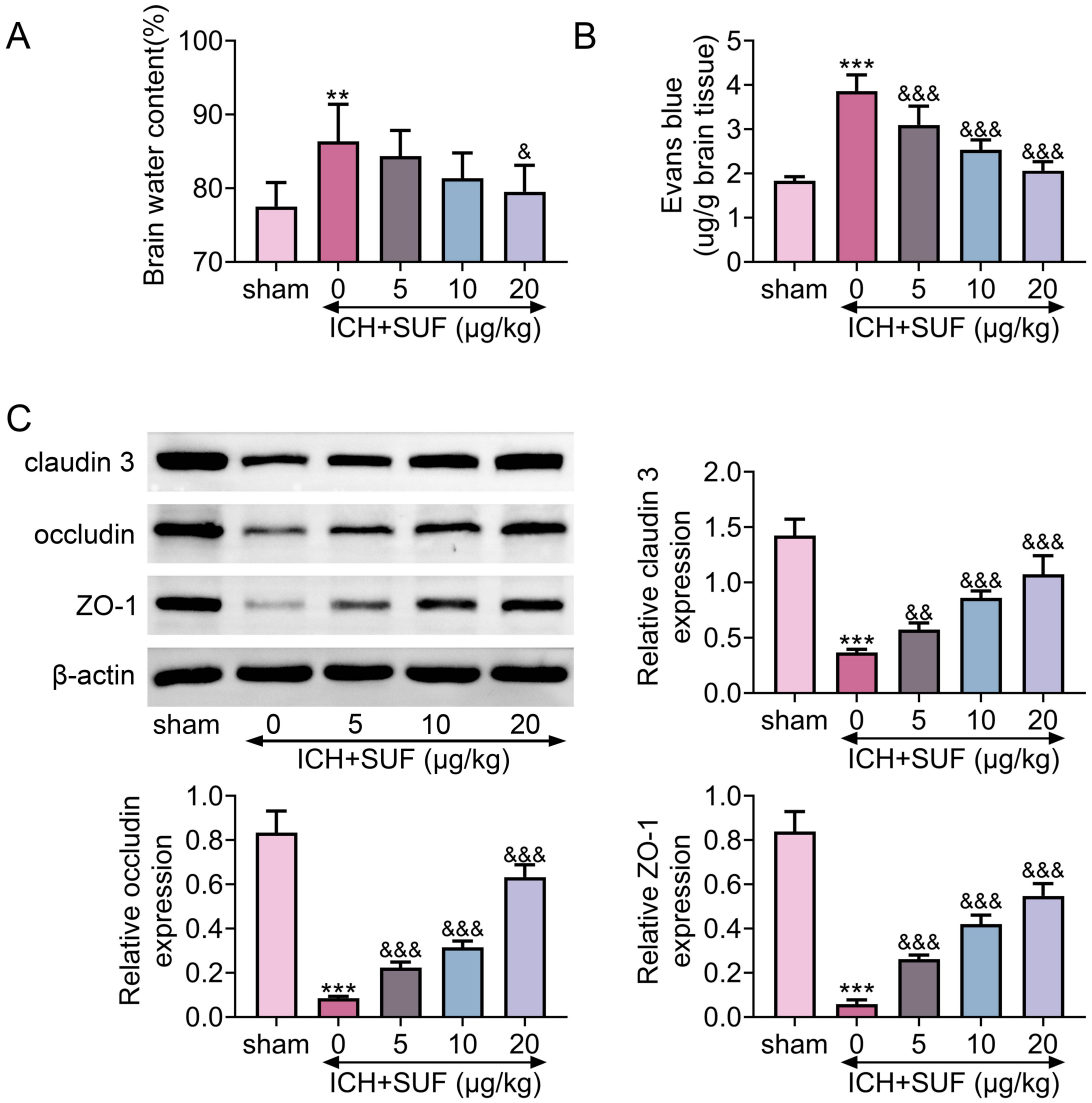

FIGURE 2. Sufentanil ameliorated blood-brain barrier injury of rats with ICH. (A) Sufentanil attenuated collagenase injection-induced increase of brain water content in rats to attenuate brain edema. N = 12. (B) Sufentanil attenuated collagenase injection-induced increase of Evans blue dye leakage in rats to attenuate blood-brain barrier injury. N = 12. (C) Sufentanil attenuated collagenase injection-induced reduction in the protein expressions of claudin 3, occludin and ZO-1 in rats. N = 12. **, *** *vs.* sham, $p < 0.01$, $p < 0.001$. $^{\&}$, $^{\&\&}$, $^{\&\&\&}$ *vs.* ICH, $p < 0.05$, $p < 0.01$, $p < 0.001$. ICH: intracerebral hemorrhage; SUF: Sufentanil; ZO-1: Zonula occludens-1.

the five components that form the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). Further results showed that sufentanil also significantly decreased the protein expression of p-p65 in rats with ICH (Fig. 3B).

3.4 Sufentanil suppressed activation of MAPKs signaling in rats with ICH

The protein expressions of p-JNK and p-P38 were significantly enhanced in the brain tissues of rats with ICH (Fig. 4). However, sufentanil dramatically reduced the expressions of p-JNK and p-P38 in rats with ICH in a dosage dependent way (Fig. 4).

3.5 Sufentanil ameliorated rat with ICH through inhibition of MAPK signaling

Treatment with MAPKs inhibitor, SB202190, significantly reduced mNSS score (Fig. 5A), decreased brain water content (Fig. 5B) and inhibited Evans blue dye leakage (Fig. 5C) in rats with ICH. Combination with SB202190 and sufentanil further down-regulated mNSS score (Fig. 5A), brain water content (Fig. 5B) and inhibited Evans blue dye leakage (Fig. 5C). Moreover, treatment with SB202190 aggravated the sufentanil-induced reduction in the protein expressions of TNF-α, IL-1β, and IL-6 in rats with ICH (Fig. 5D).

4. Discussion

Emerging evidence has shown that anesthetic agents exert neuroprotective effect on cerebral ischemia, stroke and cognitive impairment [14]. For example, sevoflurane reduced the inflammatory response and improved neurological function in ischemia/reperfusion-induced rats [15]. Volatile anesthetics regulated protein expression of tight junction proteins, and mediated the integrity of blood-brain barrier, thus participating

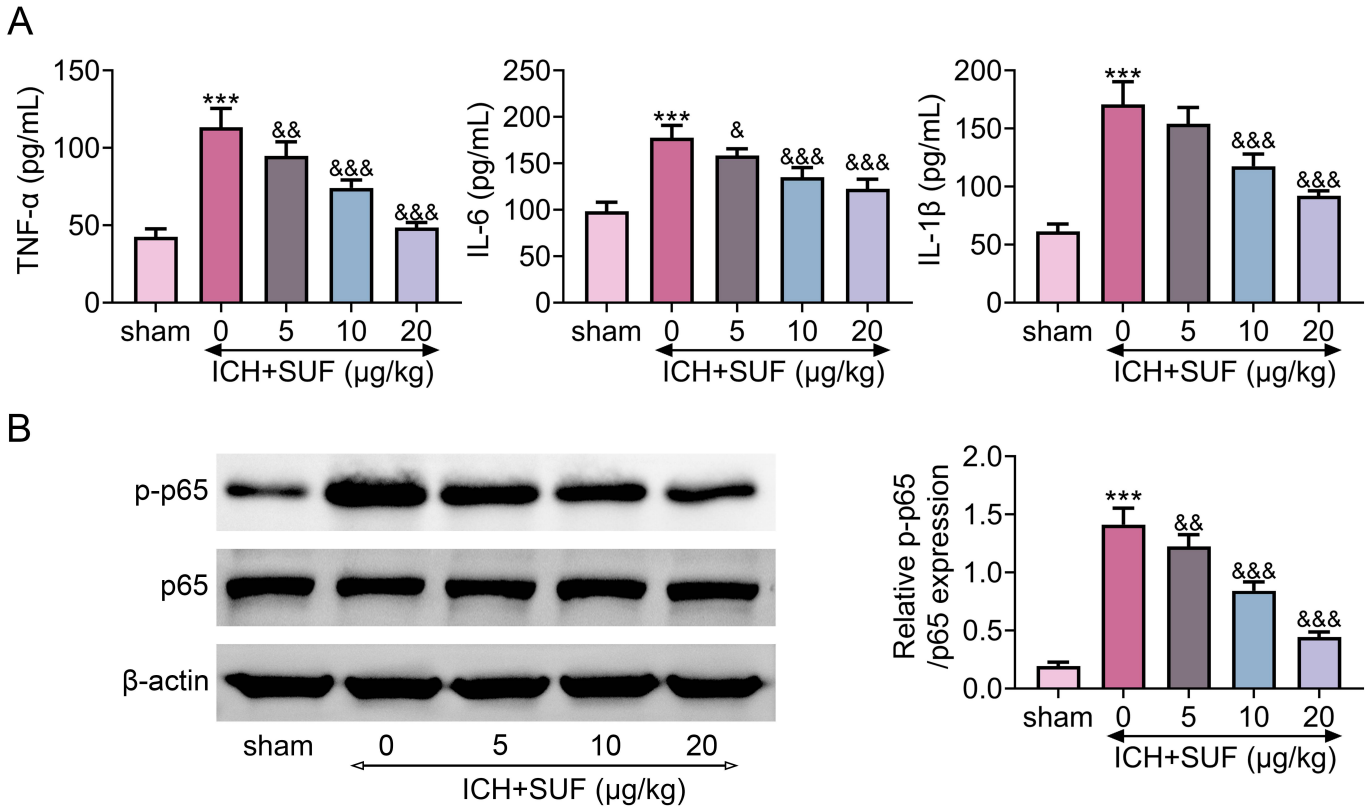

FIGURE 3. Sufentanil ameliorated neuro-inflammation of rats with ICH. (A) Sufentanil attenuated collagenase injection-induced increase of TNF-α, IL-1β, and IL-6 levels in rats to attenuate inflammation. N = 12. (B) Sufentanil attenuated collagenase injection-induced increase of p-p65 protein expression in rats. N = 12. *** *vs.* sham, $p < 0.001$. $^{\&}$, $^{\&\&}$, $^{\&\&\&}$ *vs.* ICH, $p < 0.05$, $p < 0.01$, $p < 0.001$. TNF: tumor necrosis factor; ICH: intracerebral hemorrhage; IL: interleukin; SUF: Sufentanil.

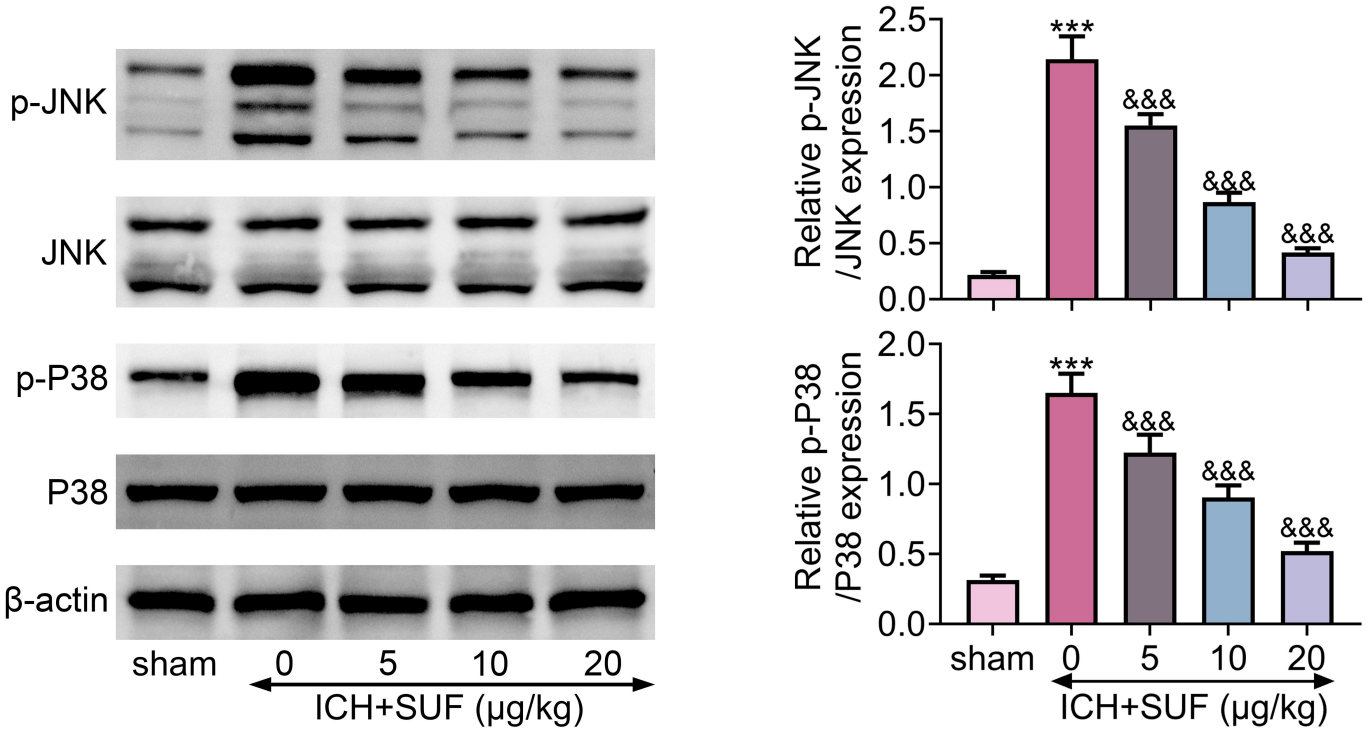

FIGURE 4. Sufentanil suppressed the activation of MAPKs signaling in rats with ICH. Sufentanil attenuated collagenase injection-induced increase of p-JNK and p-P38 protein expressions in rats. N = 12. *** *vs.* sham, $p < 0.001$. $^{\&\&\&}$ *vs.* ICH, $p < 0.001$. JNK: c-Jun N-terminal kinase; ICH: intracerebral hemorrhage; SUF: Sufentanil.

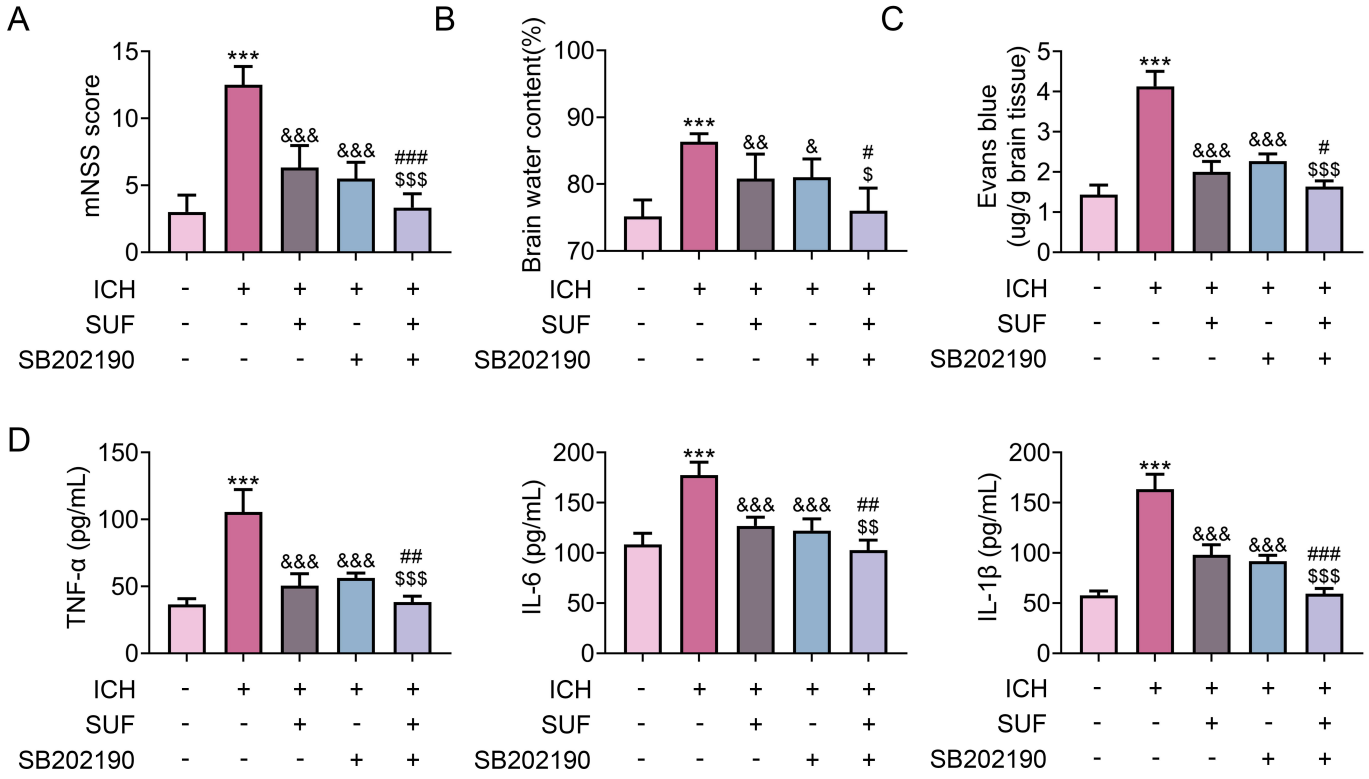

FIGURE 5. Sufentanil ameliorated rat with ICH through inhibition of MAPK signaling. (A) Treatment with SB202190 aggravated sufentanil-induced decrease of mNSS score in rats with ICH. N = 12. (B) Treatment with SB202190 aggravated sufentanil-induced decrease of brain water content in rats with ICH. N = 12. (C) Treatment with SB202190 aggravated sufentanil-induced decrease of Evans blue dye leakage in rats with ICH. N = 12. (D) Treatment with SB202190 aggravated sufentanil-induced decrease of TNF-α, IL-1β, and IL-6 levels in rats with ICH. N = 12. *** *vs.* sham, $p < 0.001$. $^{\&}$, $^{\&\&}$, $^{\&\&\&}$ *vs.* ICH, $p < 0.05$, $p < 0.01$, $p < 0.001$. $^{\#}$, $^{\#\#}$, $^{\#\#\#}$ *vs.* ICH+sufentanil, $p < 0.05$, $p < 0.01$, $p < 0.001$. $^{\$}$, $^{\$\$\$}$ *vs.* ICH+ SB202190, $p < 0.05$, < 0.001. ICH: intracerebral hemorrhage; mNSS: modified neurological severity scores; TNF: tumor necrosis factor; IL: interleukin; SUF: Sufentanil; SB202190: pyridinyl imidazole.

in the pathogenesis of cerebral edema [16]. This study found that sufentanil, an anesthetic, reduced neuroinflammation and ameliorated blood-brain barrier permeability in rats with ICH.

Previous studies have shown that injection of collagenase type IV induced neurological deficits and impaired the integrity of blood-brain barrier [17]. Therefore, collagenase injection was widely used to induce ICH rat with right-sided intrastriatal bleeding [17]. In this study, rats were injected with collagenase, and collagenase injection induced intracerebral hemorrhage with mass effects on the right lateral ventricle and corpus callosum, and increased mNSS score. Sufentanil treatment decreased mNSS score and ameliorated histological damages of ICH rat induced by collagenase injection, thereby protecting against ICH.

Disruption of the blood-brain barrier by various factors, including junctional-cytoskeletal interactions, oxidative pathways, vesicular trafficking, inflammatory modulators, and matrix metalloproteinases, is considered to be a major pathological hallmark of ischemic stroke [18]. Therefore, blood-brain barrier protection was regarded as a potential strategy for brain damage [19]. Disruption of the blood-brain barrier also promoted the entry of neuroactive agents into the perihematomal brain, influx of leukocytes, and edema formation, thus contributing to ICH-induced brain injury [20]. Decreased blood-brain barrier permeability is beneficial in reducing ICH [21]. Tight junction proteins, including claudin, occludin and ZO-1, confer the capacity of blood-brain barrier [22], and the reduction of tight junction proteins leads to the loss of blood–brain barrier integrity during the development of ICH [22]. Sufentanil has been reported to increase protein expression of collagen IV and reduce metalloproteinase 2/9 to ameliorate destruction of the blood–brain barrier [11]. In this study, sufentanil reduced brain edema, decreased Evans blue dye leakage and up-regulated claudin 3, occludin and ZO-1 in ICH rat model induced by collagenase injection. Therefore, sufentanil might protect against ICH through alleviation of blood-brain barrier permeability.

A large number of factors, including matrix metalloproteinases, complement, oxidative stress, hemoglobin breakdown products, thrombin, and inflammatory mediators, have been implicated in the pathogenesis of blood-brain barrier disruption [23]. Inhibition of neuroinflammation protected the blood-brain barrier integrity following ICH decomposition [23]. Sufentanil reduced the secretion of inflammatory cytokines and exerted anti-inflammatory effect against blood-brain barrier injury in cerebral infarction [11]. This study demonstrated that sufentanil down-regulated the levels of TNF-α, IL-1β, and IL-6 in a rat model of ICH induced by

collagenase injection, suggesting that sufentanil might exhibit anti-inflammatory effect against ICH. However, the effect of sufentanil on oxidative stress in ICH should be investigated in further research. Activation of NF-κB signaling contributed to inflammation and cell death in perihematomal brains of patients with ICH [24]. Inhibition of NF-κB signaling reduced neurological deficits and blood-brain barrier injury to ameliorate ICH [17]. Sufentanil suppressed NF-κB signaling to inhibit the proliferation and metastasis of esophageal cancer [25]. Results from this study revealed that sufentanil reduced protein expression of p-p65 to inhibited the activation of NF-κB signaling in a rat model of ICH induced by collagenase injection.

MAPKs signaling is essential for inflammation, cell proliferation and apoptosis [26–28]. MAPKs also phosphorylate distinct substrates and induce activation of NF-κB, which is essential for the secretion of pro-inflammatory factors [29]. Moreover, phosphorylation of MAPKs contributed to neuroinflammation and neuron loss in ICH [30], and inactivation of MAPKs signaling reduced brain edema and blood-brain barrier injury in rat models of ICH induced by collagenase injection [17, 31]. Sufentanil reduced protein expressions of p-JNK, p-ERK and p-P38 to inhibit inflammation and alleviate hepatic ischemia-reperfusion injury [8]. Our results also indicated that sufentanil down-regulated p-JNK and p-P38 in a rat model of ICH induced by collagenase injection to protect against ICH.

5. Conclusions

In conclusion, sufentanil improved blood-brain barrier permeability, reduced brain edema and neuroinflammation in rat models of ICH induced by collagenase injection. Sufentanil suppressed the activation of NF-κB and MAPKs signaling in the rat model of ICH. Thus, these findings suggested that sufentanil might be a novel therapeutic agent for the treatment of ICH. However, dosage of sufentanil in patients with ICH should be studied to investigate the potential benefits of sufentanil.

AVAILABILITY OF DATA AND MATERIALS

The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

HFJ, MW and LYS—designed the research study. HFJ, MW and LYS—performed the research. HFJ, MW and LYS—analyzed the data. HFJ, MW and LYS—wrote the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was obtained from the Ethics Committee of Children's Hospital of Nanjing Medical University (Approval No. 202110084-4).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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